Appln No.: 09/719,494
Amendment Dated: December 4, 2003
Reply to Office Action of June 4, 2003

REMARKS/ARGUMENTS

This is in response to the Office Action mailed June 4, 2003 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Applicants request an extension of time to make this paper timely and enclose the fee. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

Applicants note the Examiner's comments concerning lack of unity. The claims not under consideration have been noted as withdrawn. Applicants requests clarification, however, as to how dependent claims 5, 6, and 10 can be considered drawn to a different invention from the claim on which they depend. Further, the Examiner has not indicated the legal basis, under PCT Rules, for a species restriction as is being applied to claim 15. Reconsideration and withdrawal of the restriction requirement with respect to these claims, or a statement clarifying the questions noted above to facilitate a petition is requested.

The Examiner rejected claims 7 and 8 as indefinite, noting that claim 7 is a substantial duplicate of claim 3, and that claim 8 is a substantial duplicate of claim 4. Claim 7 has been amended to depend on claim 5 which overcomes this rejection. However, this amendment places the claims in the set of claims that the Examiner considers withdrawn, so the amended claims are noted as withdrawn in the listing of claims.

Claim 1 has been amended to make it clear that the non-immunogenicity or weak immunogenicity is determined in the mammalian subject to be treated. The immunogenicty of the target peptide in a foreign species, where it is not tolerated, is not relevant to the ability to generate an immune response in a species where the peptide is not recognized as foreign.

Claims 1, 2, 9, 11 and 12 are rejected as anticipated by WO 95/29193, relying on extrinsic evidence from Overwijk et al. The Examiner states that the reference "teaches a method of inducing an immune response by administering heteroclitic peptides from tumor antigens, including gp100, altered to improve peptide MHC Class I (including HLA-A2.1) binding affinity and to render the peptide capable of inducing an immune response." Overwijk is apparently cited to support a contention that gp100 is inherently weakly immunogenic, and that WO 95/29193 therefore inherently anticipates the claimed invention. Applicants respectfully submit that this argument is not consistent with the scope of the claims, and further that it is not consistent with the art.

As set forth in claim 1, the peptide that is non-immunogenic or weakly immongenic is the target peptide. To the extent that WO 95/29193 can be said to disclose peptides derived from gp100 that are non-immunogenic, or only weakly immunogenic (a fact which is not found on Page 302 of the reference as the Examiner states, since the reference has no Page 302), this is not relevant because the claim requires that **target peptide as a whole** be non-immunogenic, or only weakly immunogenic. Nothing in the Examiner's rejection supports this position. Indeed, the Overwijk reference, as cited by the Examiner, specifically states that CTL with specificity to gp100 have been detected in patients with metastatic melanoma. Thus, gp100 plainly is not non-immunogenic, nor weakly immunogenic, because a detectable CTL response is observed and gp-100-recognizing T infiltrating lymphocytes (TIL) are readily isolated. Accordingly, gp100 does not fall within the scope of the present claims. In this regard, the Examiner is asked to note the passage on Page 3 of the application in which it is stated that inherenblty non-immunogenic or only weakly immunogenic peptides "are unable to induce activation and differentiation of effector CTLs." WO 95/29193 therefore does not anticipate the present claims, because gp100 is not a target antigen within the scope of the claims.

The Examiner also rejected claims 1, 2 and 9 under 35 USC § 102 as anticipated by Lipford. In this case, the Examiner relies on a teaching of changing of a peptide from one which is non-immunogenic to one which is immunogenic, but does not address whether HPV antigen E6 is itself a target antigen within the scope of the present claims, i.e., one which is weakly immunogenic or non-immunogenic. Absent such a showing, the Examiner has not presented a complete rejection under § 102, and the rejection should be withdrawn.

The Examiner rejected claim 2 as anticipated by Dyall et al. Applicants are in the process of obtaining a *Katz* declaration which removes the paper as art, because it is not the work of another, and therefore could not have been published before the present invention was made. Accordingly, upon receipt of the declaration, this rejection should be withdrawn.

The Examiner rejected claims 1, 2, 9 and 16 as anticipated by Huard et al. "as evidenced by admission in the instant specification on page 13, lines 20-23." Without admitting that the Huard reference is in fact prior art, and reserving the right to submit a declaration antedating the document, Applicants point out that Huard does not teach anything about the induction of a cellular immune response to a target peptide, and most particularly does not teach a method of inducing a cellular immune response to HSV glycoprotein B peptide by administration of SSIEFARL (claim 16). Huard describes studies on the relationship of amino acid substitutions (and thus of physical conformation) to peptide binding with MHC Class I variants. Peptide binding may or may not be related to immunogenicity, and the reference does not show immujnization. Thus, there can be no anticipation. Further, the Examiner's explanation of this rejection is very confusing, since she seems to argue at different times that both SSIEFARL and SEIEFARL are the heteroclitic peptide, and to be arguing that the **inability** of SSIEFARL to

induce an *in vitro* CTL response in Kbm8-bearing mice teaches that it generates an *in vivo* CTL response as required in the claims.[1] Thus, the basis for the rejection is not understood.

Claims 2, 4, and 8 are rejected under 35 USC § 103 as obvious over Dyall in view of Anderson and Yewdell. This rejection is overcome by the declaration to be filed showing that the Dyall reference is not prior art.

Claims 1-4, 7-9, 11 and 12 are rejected as obvious over WO 95/29193 in view of Anderson or Yewdell. The deficiency of WO 95/29193 because gp100 is not a target antigen within the scope of the present claims has been discussed above. Anderson and Yewdell do not relate to this aspect of the claims. Accordingly, they do nothing to add or suggest the feature which is missing from WO 95/29193. The same is true of the rejection of claims 1-4, 7-9 and 11 over the combination of Lipford, Anderson and Yewdell. Furthermore, Applicants would like to point out that the present invention represents the very antithesis of obviousness. It is known in the art that peptides (such as gp100) which *in vitro* appear to generate good immune responses do not make good targets for immunization purposes because no real and effective immune response is generated. The present invention relies on the paradoxical effect observed by the present inventors and not suggested in the art that a molecule that produces poor or no immune response in the first instance actually can give rise to an effective vaccine. Thus, these rejections for obviousness should be withdrawn.

The Examiner rejected claims 1, 2, 9 and 16 as obvious over Huard et al. and claims 1-4, 7-9 and 16 as obvious over Huard et al in view of Anderson and Yewdell. Without admitting that the Huard reference is in fact prior art, and reserving the right to submit a declaration antedating the document, Applicants point out that Huard does not teach anything about the induction of a cellular immune response to a target peptide, and most particularly does not teach a method of inducing a cellular immune response to HSV glycoprotein B by administration of SSIEFARL (claim 16). Huard describes studies on the relationship of amino acid substitutions (and thus of physical conformation) to peptide binding with MHC Class I variants. The tests performed to detect CTL response are entirely *in vitro* tests, and as note don Page 12, line 25 et seq of the specification, the relationship between such tests and actual *in vivo* immunity is not clear. Indeed, the SEI species described in Huard as having CTL recognition in Kbm8-bearing mice was found to be ineffective in provide anti-tumor benefits in the present applications. (Page 14). Thus, for these reasons, and the further comments noted above in connection with the anticipation rejection.

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[1] It is noted that Table 1 also teaches the SSIEFARL does generate an *in vitro* CTL response in Kb mice.

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The Examiner rejected claims 1,2, 9 and 11-13 as obvious over WO 95/29193 in view of US 6,328,969. Applicants note that the Examiner has not addressed the reasons why the '969 patent is being applied as art in this case. It is noted that the earliest priority date in this application is before the PCT publication date, and that the US Patent itself is not available as art under 102(e) because it claims priority from a PCT application. Further, Applicants reserve the right to submit a declaration antedating the '969 patent. However, Applicants submit that on the merits the rejection should be withdrawn without need to resolve this issue.

The '969 patent teaches that certain peptides, such as gp75, are non-immunogenic or only weakly immunogenic. WO 95/29193 teaches improvement of MHC binding in peptides derived from antigens, such as gp100, which are already immunogens that promote formation of TIL that can be isolated and enriched. There is nothing in this combination of references which would lead a person skilled in the art to suspect that because one can take an immune response as measured by *in vitro* from good to better by modifying a peptide, one can also take an *in vivo* immune response from none to good. The problem that exists is not simply producing the CTL cells, but keeping them around long enough *in vivo* to do any good. *In vivo*, tolerance to self-antigens exists which defies the efforts to generate an effective immune response. The '969 patent and this application are directed to different methods for breaking this tolerance, but nothing suggests that simply doing the same old thing, as described in WO 95/29193 and other references would provide any hope for success.

For these reasons, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully Submitted,

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